TENT COOPERATION TREA

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 21243WO	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/EP 03/09790	International filing date *(day/month/year)* 02.09.2003	Priority date *(day/month/year)* 04.09.2002
International Patent Classification (IPC) or both national classification and IPC A61K38/01		
Applicant DSM IP ASSETS B.V. et al		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 12 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
13.02.2004	13.01.2005
Name and mailing address of the international preliminary examining authority: European Patent Office - P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Tx: 31 651 epo nl Fax: +31 70 340 - 3016	Authorized Officer Kanbier, D Telephone No. +31 70 340-3465

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP 03/09790

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-24 as originally filed

Claims, Numbers

1-18 as originally filed

Drawings, Sheets

1/8-8/8 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).

   ☐ the language of publication of the international application (under Rule 48.3(b)).

   ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   ☐ contained in the international application in written form.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority in written form.

   ☐ furnished subsequently to this Authority in computer readable form.

   ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   ☐ the description, pages:

   ☐ the claims, Nos.:

   ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application,

   ☒ claims Nos. 1-18, in part

   because:

   ☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (specify):

   ☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☒ no international search report has been established for the said claims Nos. 1-18, in part

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the Standard.

   ☐ the computer readable form has not been furnished or does not comply with the Standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	-
	No:	Claims	1-18
Inventive step (IS)	Yes:	Claims	-
	No:	Claims	1-18
Industrial applicability (IA)	Yes:	Claims	1-16; see separate sheet
	No:	Claims	

2. Citations and explanations

see separate sheet

Re Item I
Basis of the report

The examination is being carried out on the **following application documents:**
Text for the Contracting States:
AL AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HU IE IT LI LT LU LV MC MK NL PL PT RO SE SI SK TR

Description, pages:

1-24 as originally filed

Claims, No.:

1-18 as originally filed

Drawings, sheets:

1/8-8/8 as originally filed

The application concerns peptide fraction rich in peptides of molecular weight (MWt) lower than 500 Da (most probably corresponding to di- and tripeptides), optionally with added free amino acids (AA), and combinations thereof with a (natural) insulin sensitizer, for use in treating or preventing diabetes.
The peptide fraction alone, although effective in stimulating insulin secretion, did not lower blood glucose in late stage Type 2 diabetes patients. However, combining the peptide fraction according to the application with an insulin sensitizer had the desired blood glucose-lowering effect.
The peptide fraction is preferably obtained by hydrolysing natural protein sources.
Use of a proline (Pro) -specific (endo)protease reduces the obtained peptide size, prevents bitterness and improves water solubility of the hydrolysate.

Re Item III
Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. An International Search Report was drawn up for the present set of claims, as far as the subject matter included therein is sufficiently defined and supported by (further) claims and by examples, with due regard to the general idea underlying the application as provided by the description. For subject matter of the present application excluded from the search on this basis, no opinion with regard to novelty and inventive step is included in this preliminary examination.
   The following is a specification of the reasons for possible exclusion of part of the application's subject matter from search and thus from preliminary examination:

1.1 Present claims 1-18 relate to compositions, uses and methods involving a compound defined by reference to a desirable characteristic or property, namely sensitizing to insulin. The claims cover all compounds having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for only a very limited number of such compounds.
Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). A compound cannot be sufficiently defined by its mechanism of action and/or its pharmacological profile.

1.2 Furthermore, present claims 1-18 relate to an extremely large number of possible products by the use of the following terms: "peptide fraction", "hydrolysate" and "rich in di and/or tripeptides". The term "rich in" in itself (a relative term with no clear meaning in the technical field concerned) gives rise to a lack of clarity of the claim in which it is used. Thus a lack of clarity (and conciseness) within the meaning of Article 6 PCT arises.
Claim 10, dependent on claim 5, specifies molecular weights of below 2000 Da for at least 30 molar% of the peptides. However, claim 5 specifies a peptide mixture "rich in" peptides of less than 500 Da. Again, a lack of clarity arises; if not quite contradictory, the interdependency of these claims seems obscure.

1.3 Consequently, the International Search was carried out for those parts of the claims which appear to be clear (and concise), supported and disclosed, namely those parts relating to the products and compounds specifically claimed and used in the examples, with due regard to the description.

2. Claims 17 and 18 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion is formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

3. It is clear from the description that the combination of the claimed peptide mixture with an insulin sensitizer is essential to the definition of the invention.
Since independent claim 15 does not contain this feature it does not meet the requirement following from Article 6 PCT taken in combination with Rule 6.3(b) PCT that any independent claim must contain all the technical features essential to the definition of the invention.

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

For the assessment of the present claims 17 and 18 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Reference is made to the following documents:

D1: US-B1-6251865
D2: WO-A-9938501
D3: EP-A-1112693
D4: WO-A-9848640
D5: GB-A-2381451
D6: WO-A-9802165
D7: WO-A-0119542
D8: WO-A-0077034
D9: WO-A-0168114
D10: EP-A-1172373
D11: WO-A-9310147
D12: WO-A-0137850
D13: American Journal Of Clinical Nutrition, Bethesda, MD, Us (07-2000), 72(1), pages 96-105
D14: Derwent WPI; AN: 1994-039690 (JP(A) 5344863)
D15: US-A-4584197
D16: WO-A-0232232
D17: WO-A-0245523

D13, D16 and D17 were cited by the applicant in the description.

NOVELTY

4. The present application does not satisfy the criterion set forth in Article 33(2) PCT because the subject-matter of Claims 1-18 lacks novelty in respect of prior art documents D1-D15 as defined in the regulations (Rule 64(1)-(3) PCT). For disclosures of the documents, see below (end of Section V).

4.1 D1-D5 disclose compositions of peptide mixtures, usually hydrolysates, with free AA derived from the hydrolysis or added to the peptide mixture, in combination with insulin sensitizers as specified in present claim 11, for the treatment and/or prevention of diabetes.

4.2 D6-D11 disclose comparable compositions except that the insulin sensitizer is not one specified in present claim 11.

4.3 D12-D15 disclose comparable peptide compositions except that there is no insulin sensitizer involved. However, in view of the fact that present claim 15 is not restricted to uses of combinations of peptides with insulin sensitizers, these documents are pertinent to its novelty and that of its dependent claim 16 where appropriate (see also point 3, Section III above).

4.4 Thus D1-D15 anticipate the subject matter of the claims as follows:

D1	present claims 1, 4, 10-15, 17, 18
D2	present claims 1, 4-15, 17, 18
D3	present claims 1-5, 10-13
D4	present claims 1-5, 10-16, 18
D5*	present claims 4-6, 10, 11
D6	present claims 1-3, 12, 15, 16
D7	present claims 1, 4-6, 10, 12, 15
D8	present claims 1-3, 12-15, 17, 18
D9	present claims 1, 4-10, 12, 15, 17, 18
D10	present claims 1, 2, 4, 5, 10, 12, 15, 17, 18
D11	present claims 1, 4, 10, 12, 15, 17, 18
D12-D15	present claims 15, 16

* Although D5 was published after the claimed date of priority (04.09.2002), namely on 07.05.2003, part of the subject matter of the present application does not validly claim this priority since it has been added only at the time of International filing. For this subject matter, the relevant date becomes the International filing date, i.e. 02.09.2003. D5 accordingly is considered to be part of the state of the art for this subject matter (Rule 64.1(b)(i) PCT). The subject matter in question refers to a number of specific insulin

sensitizers claimed in present claim 11 (fenugreek, pterostilbene, a compound from grapes; ginsenoside Re from ginseng berries) and the molecular weight of the claimed peptide fractions expressed in Da, as in present claims 4-6 and 10.
D5 has been cited only against this subject matter.

INVENTIVE STEP

5. Even where novel, the present application does not satisfy the criterion set forth in Article 33(3) PCT because the subject-matter of Claims 1-18 does not involve an inventive step (Rule 65(1)(2) PCT) in view of D3, D13, D16, D17, D1-D15 and D12-D17.

5.1 According to the application, peptide mixtures as described and claimed give rise to a particularly great blood glucose lowering effect when combined with insulin sensitizers, even in late stage type II diabetes patients, where the peptide mixtures by themselves lack effectiveness (page 7).
According to the application, such peptide mixtures are known:
from D3 (including free AA Leu and Phe), as having insulinotropic activity;
from D13 (including free AA Leu, Phe and Arg), as having insulinotropic activity;
from D12 (prepared by a comparable process), as having GLP-1 inducing and beta-cell sensitivity increasing effect;
from D16 (including free AA Leu, Phe, Arg and Pro) as medicaments;
from D17 (including free AA obtained by using subtilisin and a Pro-specific endopeptidase on the proteic substrate, and carboxy-terminal Pro in >30% of the peptides), as medicaments;
from D14 (including free AA Leu and Phe), as antidiabetic compositions;
from D15 (including free AA Leu, Phe and Arg), as "insulin-like" compounds.
Thus the differences between the (closest) prior art documents D3, D13, D12, D14, D15, D16 and D17 and the present application seems to lie in the combination of the insulinotropic peptide mixtures as in D3, D13, D12, D14, D15, D16 and D17 with insulin sensitizers. However, many combinations of insulinotropic peptide mixtures and insulin sensitizers are known from the prior art (D1, D2, D4, D7, D9, D10); specific insulin sensitizers as presently claimed are also disclosed in the combinations (D1, D2, D4).

NB Although D16 and D17 do not mention insulinotropic activity or other diabetes-related effects, D3 and D13 provide indication that closely comparable peptide mixtures do have such an effect.

In the present application, no further technical effect(s) than that (those) referred to in the prior art seems to be derived from combining the claimed insulin sensitizers with insulinotropic peptide mixtures. Therefore, combining such insulin sensitizers with the peptide mixtures of D3, D13, D16, D17 would not require inventive effort. Thus present claims 1-18 lack an inventive step.

5.2 Likewise, from D1-D15, it is clear that the combination of certain insulinotropic peptides, usually hydrolysates, are known for their beneficial effect when combined with insulin sensitizers in the treatment and/or prevention of diabetes.

5.2.1 The difference between the combinations of the prior art (especially those disclosed in D1, D2, D4, D7, D9, D10, which are considered to be the closest prior art available) lies in the exact composition of the peptide fraction.

5.2.2 However, D3 and D12-D17 make it clear that such specific peptide compositions, with or without free AA, as claimed in present claims 2-10 are known for the use in treatments and/or preventions of diabetes (type II), even in combination with other actives.

5.2.3 For instance, no difference can be seen between the peptide mixtures of D16 and D17 and those of the present application. Although D16 and D17 do not specifically refer to antidiabetic applications, the use of the peptide mixtures in medicaments is clearly disclosed. Thus for use in first medical compositions it would not require an inventive step to replace the peptide mixtures of D1, D2, D4, D7, D9, D10 with those of D3, D13, D12, D14, D16 or D17 (claims 1-10,12,13), while application in diabetes is also indicated in D3 (insulinotropic activity), D13, D12, D14 and D15 (claims 14, 17, 18). Furthermore, in view of the generally known applicability of such peptide mixtures in antidiabetic applications (see D13) in view of their insulinotropic effect (D3), the use of the peptide mixtures of D16 and D17 in antidiabetic combinations with an insulin sensitizer also does not seem inventive (claims 14, 17, 18).

MINOR OBJECTIONS

Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in D1-D5 is not mentioned in the description, nor are these documents identified therein.

DISCLOSURES OF THE VARIOUS PRIOR ART DOCUMENTS

D1 Peptides used to increase serum and tissue levels of insulin-like growth factor in those with hyperglycemic, obesity-related, etc., disorders e.g. diabetic patients (exs. 3,6; col. 33); comprising fully defined 11-20 amino acid sequences (I)-(VI), which have non-free Leu, Arg and Pro (but not C-terminal Pro). Also compositions comprising (I)-(VI) and a thiazolidinedione (claimed) or biguanide. See especially col. 3, line 12 and col. 31, lines 52-55.

D2 Modifying glucose metabolism by administering a composition comprising boronyl peptidomimetic of a peptide selected from Pro-Pro, Ala-Pro, and (D)-Ala-(L)-Ala (also tripeptides thereof with Pro at C-terminal) (cl.1,4,12; p.15,16,33). Mechanism: inhibitors of a dipeptidylpeptidase. Also used conjointedly with e.g. metformin, acarbose, glibenclamide, in general also with insulinotropic agents (p45-46). See especially page 7, lines 34-35 and page 33, lines 14-16

D3 Enhancer of blood insulin response (insulinotropic effect): protein hydrolysates of 2-40 AA in length, pref. 3-20 AA (page 2, lines 44-46) + Leu and Phe (as free AA which improve insulinotropic effect, page 4, lines 24-25) in combination with the high carbohydrate intake associated with physical exercise, or to delay exhaustion during exercise. No therapy has been specifically described but the insulinotropic effect was tested (Table 1). Examples: commercial hydrolysates having an average of 4.1 and 6.4 AA chain length. Example 3 shows the hydrolysate with 6.4 AA chain length, with free Leu and Phe and containing vit B3 (=niacin), as an enteral feeding composition for use in hospital environment.

D4 Ion exchanged and hydrolysed whey protein has no insulin; it is used to make an infant formula not giving rise to juvenile (type I) diabetes. Hydrolysis breaks down the insulin to oligopeptides of at most 5 AA (p.7). Example 7 discloses a composition of the hydrolysate + glucose + maltodextrin + niacin + biotin + L-tyr + L-phe (free AA are added to the composition, not from hydrolysate).

D5 Pharmaco-dietary preparation for reducing excess weight and associated disorders e.g. diabetes, comprises hydrolysate of amino acids and/or peptides, and beta-alanine. Page 1: it has marked organoleptic virtues. Example 1 specifies a casein hydrolysate with a cut-off value of 3000 Da. Example 2 contains the hydrolysate of example 1 and also contains niacin, Cr, Va; the peptides also have free AA and are especially rich in Leu.

D6 Reducing appetite and carbohydrate craving by using tryptophan, phenylalanine, tyrosine and histidine. Hydrolysed protein is utilized as a natural tryptophan source, together with an insulin producing carbohydrate. Diabetes is said to be associated to obesity. Tyr and Phe may be added. Also (p.6) hydrolysis permits delivery of free AA.

D7 Yeast extract, cut off UF at 1000 Da (process: fig.1, page 5, pages 12-13), contains Cr; for treating type II diabetes. Tests: par. 5.5.3-4 (pages 20-21). Also Cr compounds for treating diabetes type II (cl. 34); Cr is hypoglycaemic (par. 5.5.1, page 18). Cr-GSH complex (page 15, par. 5.3); GSH is a tripeptide of Cys-Glu-Gly.

D8 Hypoglycaemic antidiabetic compositions for treating diabetes comprise fish or soy proteins and/or amino acids, both from hydrolysis. Claims: only the proteic composition, no insulin sensitizer (present claim 15); however, in table 1 a vitamin mix is included with niacin, biotin, chromium, etc.

D9 Pure tripeptides are ACE inhibitors, usually having Pro at the end; also claimed for diabetes (cl.19). "Pure" also means more than 50% of the proteic fraction is tripeptides, pref. more than 95% (page 8, lines 12-24). All examples: synthesized tripeptides. Added to foods, including beverages (p.8, l.25-p.9, l.4; p.14, l.20-28). Food contains e.g. potato starch, sucrose, corn starch (p.14); these are insulin sensitizers.

D10 Zinc-oligopeptide association (cl.1) for activating insulin in diabetics (page 2, lines 10-13, 18, 22-23, 45-46). The oligopeptide has 6 AA (glu, gly, lys, ala, asp, and arg). The oligopeptide is made by enzymatic hydrolysis of protein (page 2, lines 39-50; claim 3). Zinc acts as the insulin sensitizer.

D11 Amylin antagonists are opt. modified peptide A; opt. modified peptide B or (3) opt. modified peptide C. They are used for treatment of type 2 diabetes, impaired glucose tolerance, obesity and insulin resistance. They are formulated for parenteral, nasal or oral administration, opt. with another hypoglycaemic e.g. as a sulphonylureas; the latter are considered to fall within the (not completely clear) term "insulin sensitizers" of present claim 1.

D12 Milk protein hydrolysate, esp. whey protein hydrolysate or caseinoglycomacropeptide (example 1: cut-off 3000 Da) for treatment of diabetes or syndrome X (claim 7). The hydrolysate is capable of inducing release of glucagon-like peptide-1 (GLP-1) (page 2). It also increases beta-cell sensitivity (page 4). Another protein hydrolysate, meat hydrolysate, did not induce such an effect on GLP-1 production. Processes for obtaining the hydrolysates on pages 8-9. It is likely that such processes will result in peptide mixtures falling within the scope of present claims 2-10 and 16.

D13 Proteic mixtures of hydrolysates with free AA: Table 1: wheat hydrolysate + Phe + Leu in a glucide (carbohydrate) containing oral composition (test drinks 9 and 10; 10 has added arginine, which turns out not to add any insulinotropic effect). The proteic hydrolysate works better than non-denaturated protein (tested with casein). The combination hydrolysate + free AA (leu, phe, tyr) is even better since it provides insulinotropic effect of free AA without G.I. discomfort. P.96: type II diabetes, early stages of-, with decreasing insulin sensitivity: combination with insulin sensitizer obvious.

D14 Antidiabetic composition of a protein hydrolysate and free AA (including Leu and Phe); as food, drink or therapeutic composition.

D15 (Shell-)fish extract made by treating mackerel with proteinases from Bacillus subtilis and koji (example 1, column 6), has a content of free Leu, Tyr, Phe and Arg (Table 1). It has (amongst other functions) and "insulin-like" function (column 1, example 4).

D16 Protein hydrolysates are prepared from the same proteic sources with the same process(es). Free AA are most preferably Leu, Pro, Phe, Arg, (Lys, Glu), for taste reasons (page 8). Reference to therapy is on page 1: protein hydrolysates in metabolic disorders. Proteases used include Pro-specific endopeptidases and subtilisin (although not in a preferred combination) (page 12).

D17 Pro-rich terminal peptides are prepared from the same proteic sources with the same process(es). Claim 17: Pro-specific endoprotease + subtilisin + carboxypeptidase on the proteic substrate. Application in several therapies s envisaged on pages 7-8; no diabetes but various other diseases, in relation to Pro-rich peptides.

FURTHER OBJECTIONS

Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in D1-D12, D14 and D15 is not mentioned in the description, nor are these documents identified therein.